

Pring
10/509605

DT04 Rec'd PCT/PTO 27 SEP 2004

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

I, ADRIAN PAUL BROWN, M.A., M.I.L., M.I.T.I., declare

1. That I am a citizen of the United Kingdom of Great Britain and Northern Ireland, residing at 5 Gilbert Road, London, SE11 4NZ.
2. That I am well acquainted with the French and English languages.
3. That the attached is a true translation into the English language of the certified copy of French Patent Application No. 02 04222 filed on 5 April 2002.
4. That all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that wilful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such wilful false statements may jeopardise the validity of the patent application in the United States of America or any patent issuing thereon.

DECLARED THIS 21st DAY OF JULY 2004

A.P. Brown

A P BROWN



NATIONAL INSTITUTE
FOR INDUSTRIAL
PROPERTY

10/509605
DT04 Rec'd PCT/PTO 27 SEP 2004

PATENT OF INVENTION

UTILITY CERTIFICATE - CERTIFICATE OF ADDITION

OFFICIAL COPY

The Director General of the National Institute for Industrial Property certifies that the attached document is the true certified copy of an application for an Industrial Property Right filed at the Institute.

Issued in Paris, 23 APR. 2004

For the Director General of the
National Institute for Industrial Property,
The Head of the Patents Department

(signature)

Martine PLANCHE

NATIONAL
INSTITUTE FOR
INDUSTRIAL
PROPERTY

NATIONAL PUBLIC INSTITUTION

DB 267/220104

HEAD OFFICE

26 bis, rue de Saint-Petersbourg
75800 PARIS cedex 08
Telephone: 33 (0)1 53 04 53 04
Facsimile: 33 (0)1 53 04 45 23
www.inpi.fr

CREATED BY LAW NO. 51-444 OF 19th APRIL 1951

First filing

10/509605

DT04 R PCT/PTO 27 SEP 2004

INPI

National
Institute for
Industrial Property
26bis, rue de Saint Pétersbourg
75800 Paris Cedex 08
Telephone: 01 53 04 53 04
Facsimile: 01 42 94 86 54

PATENT OF INVENTION
UTILITY CERTIFICATE
Intellectual Property Code - Book VI

cerfa
No. 11354*01

REQUEST FOR GRANT 1/2

Reserved for INPI

This form is to be completed legibly in black ink DB 540 W /260899

DEPOSITION OF DOCUMENTS DATE 5 APRIL 2002 PLACE 75 INPI PARIS NATIONAL REGISTRATION NO. GIVEN BY THE INPI 0204222 FILING DATE GIVEN BY THE INPI 5 APR. 2002		1 NAME AND ADDRESS OF THE APPLICANT OR OF THE AUTHORISED AGENT TO WHOM CORRESPONDENCE MUST BE ADDRESSED LES LABORATOIRES SERVIER Direction Brevets 1, rue Carle Hébert 92415 COURBEVOIE Cedex FRANCE	
Your references for this file (optional) 18886-ASP			
Confirmation of a deposit by facsimile		<input type="checkbox"/> No. given by INPI to the facsimile	
2 NATURE OF THE APPLICATION		Mark one of the following 4 boxes	
Patent application		<input checked="" type="checkbox"/>	
Application for a Utility Certificate		<input type="checkbox"/>	
Divisional application <i>Initial patent application or initial utility certificate application</i>		<input type="checkbox"/>	
		No. Date	
		No. Date	
Conversion of a European Patent Application <i>Initial patent application</i>		<input type="checkbox"/>	
		No. Date	
3 TITLE OF THE INVENTION (maximum 200 characters or spaces) NEW ASSOCIATION OF AN ANTITHROMBOTIC AND ASPIRIN.			
4 DECLARATION OF PRIORITY OR REQUEST FOR THE BENEFIT OF THE FILING DATE OF A PRIOR FRENCH APPLICATION		Country or organisation No. Date Country or organisation No. Date Country or organisation No. Date <input type="checkbox"/> If there are other priorities, mark the box and use the "Continuation" form	
5 APPLICANT		<input type="checkbox"/> If there are other Applicants, mark the box and use the "Continuation" form	
Surname or company name		LES LABORATOIRES SERVIER	
Forenames			
Legal nature			
SIREN No.			
APE-NAF Code			
Address	Street	1, rue Carle Hébert	
	Postal code and town	92415	COURBEVOIE cedex
Country		FRANCE	
Nationality		FRENCH	
Telephone no. (optional)		01.55.72.60.00	
Facsimile no. (optional)		01.55.72.72.13	
E-mail address (optional)			

INPINational
Institute for
Industrial Property**PATENT OF INVENTION
UTILITY CERTIFICATE**

REQUEST FOR GRANT 2/2

Reserved for INPI

DEPOSITION OF DOCUMENTS			
DATE 5 APRIL 2002			
PLACE 75 INPI PARIS			
NATIONAL REGISTRATION NO. GIVEN BY THE INPI 0204222		DB 540 W /260899	
Your references for this file: (optional)		18886-ASP	
6 AUTHORISED AGENT			
Surname		JAGUELIN-GUINAMANT	
Forename		Sylvie	
Practice or company		LES LABORATOIRES SERVIER	
No. of standing power of attorney and/or of contractual bond			
Address	Street	1, rue Carle Hébert	
	Postal code and town	92415	COURBEVOIE Cedex (France)
Telephone no. (optional)		01.55.72.68.07	
Facsimile no. (optional)		01.55.72.72.13	
E-mail address (optional)			
7 INVENTOR(S)			
The inventors are the Applicants		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No In this case, supply a separate designation of inventorship	
8 SEARCH REPORT		For a patent application only (including division and conversion)	
immediate drawing up or deferred drawing up		<input checked="" type="checkbox"/> <input type="checkbox"/>	
Payment of the fees in instalments		Payment in three instalments, for natural persons only <input type="checkbox"/> Yes <input type="checkbox"/> No	
9 REDUCTION IN FEES		For natural persons only <input type="checkbox"/> Requested for the first time for this invention (attach a notice of non-imposition) <input type="checkbox"/> Requested prior to this deposit (attach a copy of the admissibility decision for this invention or indicate its reference)	
If you have used the "Continuation" form, indicate the number of pages attached			
10 SIGNATURE OF THE APPLICANT OR OF THE AUTHORISED AGENT (Name and position of signatory) (signature) S. JAGUELIN-GUINAMANT, Patent Engineer		STAMP OF THE PREFECTURE OR OF THE INPI [signature] L. GUICHET	

The new invention relates to a new association of an antithrombotic and aspirin and to pharmaceutical compositions containing them.

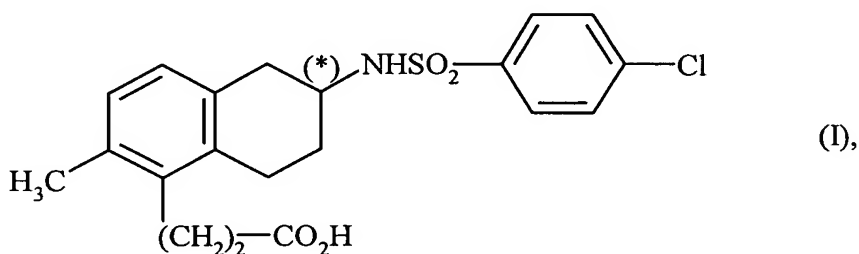
More specifically, the present invention relates to the association of a TP receptor antagonist and aspirin.

- 5 Thromboxane A₂ (TXA₂) is an unstable metabolite of arachidonic acid which is involved in the pathogenesis of numerous disorders of blood circulation. Thromboxane A₂ is a powerful platelet activator but is also a powerful vasoconstrictor which has cell proliferative and pro-adhesive properties.

- 10 TXA₂ and other metabolites of arachidonic acid such as endoperoxide (PGH₂), HETEs and isoprostanes exert their action by way of common receptors called TP receptors.

- Numerous research studies have recently been carried out with the aim of preventing circulatory disorders caused by the excessive production of thromboxane A₂. Among such antagonists, those described in the Patent Specification EP 648 741 have been found to be powerful and selective antagonists of TP receptors, to be active *via* the oral route and to have a long duration of action.
- 15

More specifically, the compound (A) of formula (I) :



in racemic form or in the form of an optically pure isomer, and also pharmaceutically acceptable salts thereof, has been found to be a powerful antithrombotic.

- 20 That compound selectively inhibits blood platelet aggregation caused by activation of the TP receptors and, moreover, has anti-atherosclerotic properties after administration by the oral route.

We have now found that the association of compound A and aspirin allows, surprisingly, a synergy to be obtained in terms of antithrombotic activity.

It has been described in the literature that certain associations of anti-platelet aggregation agents such as dipyridamole and aspirin have additive effects and that such an association
5 has been shown to be of value in the prevention of cerebral vascular accidents.

Other associations of anti-platelet aggregation agents with aspirin have been described in the literature. In view of the fact that those anti-aggregation agents act on platelet aggregation pathways (such as the purinergic pathways, ADP) which are different from those of aspirin, which acts via the pathway of arachidonic acid metabolism, it was
10 expected that additive effects on the activity of those compounds would be observed.

The association to which the present invention relates is, for its part, completely different: compound A and aspirin both act on the arachidonic acid metabolism pathways: the former acts by irreversibly inhibiting the cyclo-oxygenases, which convert arachidonic acid into endoperoxide (PGH₂) and the latter acts by opposing the activity of certain metabolites of arachidonic acid such as thromboxane A₂, the isoprostanes and endoperoxide.
15

It has been found, surprisingly, that the association of compound A and aspirin allows substantial synergy to be obtained in terms of activity, which could not have been foreseen from any teaching of the literature.

That synergistic effect has been demonstrated in an arterial thrombosis test in the guinea-pig. In the course of that test it was shown that the antithrombotic activity of compound A
20 is potentiated in the presence of aspirin and increases in extremely substantial and entirely unforeseeable manner.

In the associations according to the invention, compound (A) and aspirin can be present in the form of pharmaceutically acceptable salts.

Among the addition salts of compound (A), there may be mentioned, without implying any limitation, addition salts with a pharmaceutically acceptable base, such as sodium, potassium, *tert*-butylamine and diethylamine salts etc..

Preference will be given to use of the sodium salt.

- 5 Among the addition salts of aspirin, there may be mentioned, without implying any limitation, addition salts with a pharmaceutically acceptable acid, such as acetate, benzoate, fumarate, maleate, citrate, tartrate, the lysine salt etc..

In the associations according to the invention, compound (A) preferably has the absolute configuration (R).

- 10 The present invention relates also to pharmaceutical compositions comprising an association of compound (A) and aspirin, where appropriate in the form of pharmaceutically acceptable salts, together with one or more appropriate, inert, non-toxic excipients.

- 15 Among the pharmaceutical compositions according to the invention there may be mentioned more especially those that are suitable for oral, parenteral or nasal administration, tablets or dragées, sublingual tablets, gelatin capsules, lozenges, suppositories, creams, ointments, dermal gels etc..

The dosage can be varied according to the nature and severity of the condition, the administration route and also the age and weight of the patient.

- 20 In the compositions according to the invention, the amounts of active ingredients are in the range from 1 to 300 mg for compound (A) and from 100 to 1000 mg for aspirin.

The compositions according to the invention are accordingly useful in the treatment of atherothrombotic illnesses involving the activation of TP receptors and/or the formation of metabolites and also in the treatment of consequences of those illnesses. Those pathologies

include, without implying any limitation, stable or unstable angina, endothelial or vascular dysfunction accompanying illnesses such as hypertension, diabetes, heart failure, disorders of the cardiovascular or cerebrovascular system, or thrombo-embolic disorders associated especially with atherosclerosis.

5 The associations according to the invention have been studied and the synergy effect has been demonstrated in an arterial thrombosis test in the guinea-pig.

This test is based on the model initially described by Roux *et al.* (Thromb Haemost 71 : 252-256, 1994). The guinea-pigs are anaesthetised using ketamine + xylazine (90 + 12) mg.kg i.m.. The trachea is cannulated and spontaneous respiration by the animals
10 maintained. The jugular vein is cannulated, allowing the intravenous administration of the compounds being tested. The carotid artery is isolated, and a Doppler probe is installed allowing the arterial blood flow to be measured. After stabilisation, a lesion to the artery wall is produced by means of a clip applied distally to the Doppler probe. Subsequent to that lesion, the blood flow decreases. When the flow reaches zero, the artery is lightly
15 shaken, which allows the flow to be restored. The thrombosis process continues, leading again to the flow reducing and ceasing. The thrombotic phenomena accordingly result in cyclic flow reductions (CFR), which are observed over a period of 20 minutes. After that period, the animal is treated, or not, with compound (A), and the CFR are again observed for a period of 20 minutes. The experiments are carried out in control animals or in animals
20 treated by the intravenous route with aspirin (2 mg/kg).

This study was carried out using the sodium salt of the (R) isomer of compound (A).

The results show that 10 ± 1 CFR/20 min are observed in the untreated animals. Compound (A), administered by the intravenous route, reduces the CFR in dose-dependent manner; a significant effect is obtained from the 0.3 mg/kg dose (5 ± 2 CFR/20 min).
25 Almost total inhibition (2 ± 2 CFR/20 min) is obtained with a dose of 1 mg/kg.

In the animals treated with aspirin, 8 ± 1 CFR/20 min are observed; that value is not different from that obtained in the control animals.

Compound (A), administered by the intravenous route to animals already treated with aspirin, reduces the CFR in dose-dependant manner; a significant effect is now obtained

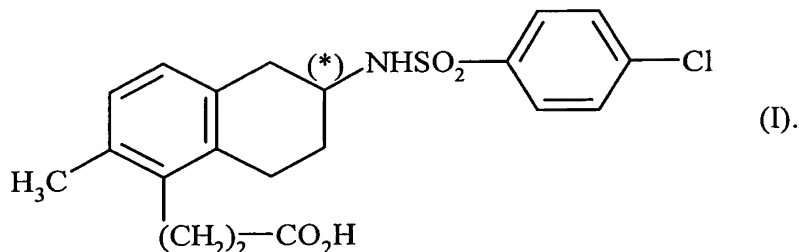
from the 0.01 mg/kg dose (5 ± 1 CFR/20 min), and almost complete inhibition is obtained with a dose of 0.1 mg/kg (2 ± 1 CFR/20 min).

Those results firstly show the powerful antithrombotic activity of compound (A), which is active from the 0.3 mg/kg dose.

- 5 Moreover, in the presence of a dose of aspirin which does not bring about an antithrombotic effect, the antithrombotic activity of compound (A) is potentiated and increased by at least 30 times. In fact, that effect is observed from the 0.01 mg/kg dose, which means that there exists a very substantial synergy effect when the two active ingredients are administered simultaneously.

CLAIMS

1- Association of compound (A) of formula (I), optionally in the form of an optical isomer or one of its pharmaceutically acceptable salts, and aspirin, or one of its pharmaceutically acceptable salts :



2- Association according to claim 1, characterised in that compound (A) is in (R) configuration optical isomer form.

3- Association according to either claim 1 or claim 2, characterised in that compound (A) is in the form of a sodium salt.

4- Pharmaceutical composition comprising as active ingredients an association of compound (A), optionally in the form of an optical isomer or one of its pharmaceutically acceptable salts, and aspirin, or one of its pharmaceutically acceptable salts, in combination with one or more pharmaceutically acceptable, inert excipients or carriers.

5- Pharmaceutical composition according to claim 4, characterised in that compound (A) is in (R) configuration optical isomer form.

6- Pharmaceutical composition according to either claim 4 or claim 5, characterised in that compound (A) is in sodium salt form.

7- Pharmaceutical composition according to any one of claims 4 to 6, characterised in that the amounts of active ingredients are in the respective ranges of from 1 to 300 mg for compound (A) and from 10 to 1000 mg for aspirin.

8- Pharmaceutical composition according to any one of claims 4 to 7, for use in the treatment of atherothrombotic illnesses involving the activation of TP receptors and/or the formation of metabolites and also in the treatment of consequences of those illnesses.

Received on 24/04/02

DT04 Rec'd PCT/PTO 27 SEP 2004

INPINational
Institute for
Industrial Property**PATENT OF INVENTION
UTILITY CERTIFICATE**
Intellectual Property Code - Book VIcerfa
No. 11235*02PATENTS DEPARTMENT
26bis, rue de Saint Pétersbourg
75800 Paris Cedex 08
Telephone: 01 53 04 53 04
Facsimile: 01 42 93 59 30**DECLARATION OF INVENTORSHIP**

Page No. 1 / 2

(if the applicant is not the inventor or not the only inventor)

This form is to be completed legibly in black ink DB 113 W /260899

Your references for this file (optional)		18886-ASP	
NATIONAL REGISTRATION NO.		0204222	
TITLE OF THE INVENTION (maximum 200 characters or spaces) NEW ASSOCIATION OF AN ANTITHROMBOTIC AND ASPIRIN.			
APPLICANT(S): LES LABORATOIRES SERVIER 1, rue Carle Hébert 92415 COURBEVOIE Cedex FRANCE			
DESIGNATE(S) AS INVENTOR(S) : (Indicate at the top right-hand side "Page No. 1/1". If there are more than three inventors, use an identical form and number each page indicating the total number of pages).			
Surname		VERBEUREN	
Forenames		Tony	
Address	Street	60 bis, rue Aristide Briand	
	Postal code and town	78540	VERNOUILLET (France)
Belonging company (optional)			
Surname		LAVIELLE	
Forenames		Gilbert	
Address	Street	1, avenue Lily	
	Postal code and town	78170	LA CELLE SAINT CLOUD (France)
Belonging company (optional)			
Surname		CIMETIERE	
Forenames		Bernard	
Address	Street	37, cours de Vincennes	
	Postal code and town	75020	PARIS (France)
Belonging company (optional)			
DATE AND SIGNATURE(S) OF THE APPLICANT(S) OR OF THE AUTHORISED AGENT (Name and position of signatory) 5th April 2002 (signature) S. JAGUELIN-GUINAMANT, Patent Engineer			

Law No. 78-17 of 6 January 1978 relating to information processing, data files and rights applies to the responses made on this form. It guarantees right of access to and correction of the data concerning you at the INPI.

Received on 24/04/02

INPI

National
Institute for
Industrial Property

**PATENT OF INVENTION
UTILITY CERTIFICATE**
Intellectual Property Code - Book VI

cerfa
No. 11235*02

PATENTS DEPARTMENT
26bis, rue de Saint Pétersbourg
75800 Paris Cedex 08
Telephone: 01 53 04 53 04
Facsimile: 01 42 93 59 30

DECLARATION OF INVENTORSHIP

Page No. 2 / 2

(if the applicant is not the inventor or not the only inventor)

This form is to be completed legibly in black ink DB 113 W /260899

Your references for this file (optional)		18886-ASP	
NATIONAL REGISTRATION NO.		0204222	
TITLE OF THE INVENTION (maximum 200 characters or spaces) NEW ASSOCIATION OF AN ANTITHROMBOTIC AND ASPIRIN.			
APPLICANT(S): LES LABORATOIRES SERVIER 1, rue Carle Hébert 92415 COURBEVOIE Cedex FRANCE			
DESIGNATE(S) AS INVENTOR(S) : (Indicate at the top right-hand side "Page No. 1/1". If there are more than three inventors, use an identical form and number each page indicating the total number of pages).			
Surname		VALLEZ	
Forenames		Marie-Odile	
Address	Street	4, allée des Charmilles	
	Postal code and town	77420	CHAMPS SUR MARNE (France)
Belonging company (optional)			
Surname			
Forenames			
Address	Street		
	Postal code and town		
Belonging company (optional)			
Surname			
Forenames			
Address	Street		
	Postal code and town		
Belonging company (optional)			
DATE AND SIGNATURE(S) OF THE APPLICANT(S) OR OF THE AUTHORISED AGENT (Name and position of signatory) 5th April 2002 (signature) S. JAGUELIN-GUINAMANT, Patent Engineer			

Law No. 78-17 of 6 January 1978 relating to information processing, data files and rights applies to the responses made on this form. It guarantees right of access to and correction of the data concerning you at the INPI.